PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 26 April 2001 (26.04.01)	
International application No. PCT/EP00/08011	**Applicant's or agent's file reference** sch10069pct
International filing date (day/month/year) 16 August 2000 (16.08.00)	**Priority date** (day/month/year) 16 August 1999 (16.08.99)
Applicant SUZUKI, Tsuneji et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

05 March 2001 (05.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Nestor Santesso Telephone No.: (41-22) 338.83.38

CK

WO 01/12193
PCT/EP00/08011

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
DÖRRIES, FRANK-MOLNIA & POHLMAN
Triftstrasse 13
80538 München
ALLEMAGNE

Deadline:

RECEIVED
05. März 2001
df-mp
Dörries, Frank-Molnia & Pohlman
Patents · Trademarks · Designs

IMPORTANT NOTICE
Reminder:

Date of mailing (day/month/year)		
22 February 2001 (22.02.01)		
Applicant's or agent's file reference		
sch10069pct		
International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/08011	16 August 2000 (16.08.00)	16 August 1999 (16.08.99)
Applicant		
SCHERING AKTIENGESELLSCHAFT et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES, FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK, MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   22 February 2001 (22.02.01) under No. WO 01/12193

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

3839372

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
sch10069pct		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08011	16/08/2000	16/08/1999
International Patent Classification (IPC) or national classification and IPC A61K31/4406		
Applicant SCHERING AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/03/2001	16.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Siatou, E Telephone No. +49 30 25901 327

Form PCT/IPEA/409 (cover sheet) (January 1994)

REC'D 22 OCT 2001
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
sch10069pct		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08011	16/08/2000	16/08/1999
International Patent Classification (IPC) or national classification and IPC A61K31/4406		
Applicant SCHERING AG		

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   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/03/2001	16.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Siatou, E Telephone No. +49 30 25901 327

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08011

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17	as originally filed	

Claims, No.:

1-17	as received on	12/03/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-2, 4-17.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 14-15
	No:	Claims	1, 4-13, 16-17
Inventive step (IS)	Yes:	Claims	2, 14-15
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-2, 4-17
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item IV

Lack of unity of invention

The examining authority found that amended claims 1-17 as received on 12/03/2001 lack unity of invention and invited the Applicant to pay additional fees.
The separate inventions are:

1) claims 1, 4-17 (invention 1) relating to pharmaceutical compositions comprising i) a benzamide derivative and ii) one or more compounds selected from the group consisting of an inorganic salt, an amino compound and an inorganic substance together with disintegrants, binders, lubricants, coating agents and solvents.

2) claims 2, 4-17 (invention 2)Independent claim 2 relates to pharmaceutical compositions containing i) a benzamide derivative and ii) at least one of mannitol, partially gelatinised starch, sodium carboxymethyl starch, HPC, HPMC and dimethylacetamide, and

3) claims 3, 4-17 (invention 3) relating to to pharmaceutical compositions containing i) a benzamide derivative dissolved in ii) propylene glycol as solvent.
The Applicant has paid additional fees and asked for the examination of inventions 1 and 2.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:
D1: EP-A-847992

For claims 1, 4-17 (invention 1) the following comments on novelty and inventive step apply:

Document D1, which is considered to represent the most relevant state of the art, discloses (cf. claims 1,14-16, 21-23 and page 46, lines 4-40) benzamide derivatives containing pharmaceutical compositions as well as one or more excipients, disintegrants, binders, lubricants, coating agents, solvents. The excipients used depend

on the pharmaceutical form. One of the listed possible disintegrators is sodium alginate and/or calcium carbonate as excipient.
Tthe subject matter of claim 1, as well as that of dependent claims 4-13 and 16-17, therefore is not novel (Art. 33(2) PCT).

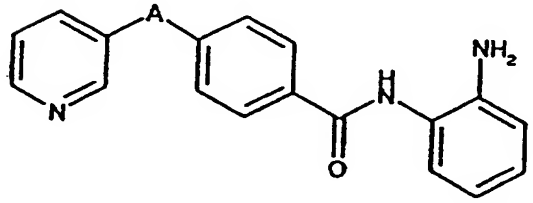
For claims 2, 4-17 (invention 2) the following comments on novelty and inventive step apply:
The document D1 is regarded as being the closest prior art to the subject-matter of claim 2, and shows (the references in parentheses applying to this document): pharmaceutical formulations comprising benzamide derivatives and excipients, disintegrants, binders, lubricants, solvents (claims 1, 14-16, 21-23 and page 46, lines 4-40).
The subject-matter of claim 2 therefore differs from this known formulations of D1 in that one or more compounds selected from D-mannitol, partially geltinized starch, carboxymethylstarch sodium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose and dimethylacatamide must be present.
The subject-matter of claim 2 is therefore novel (Article 33(2) PCT).
The applicant has also demonstrated that the presence of these compounds leads to decreased degradation of the benzamide derivative in the formulation and hence to incresed stability.
The subject matter of claim 2 is therefore inventive (Art. 33(3) PCT).

Claims 4-17 are dependent on claim 2 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

Claims 2 and 4-17 are industrially applicable (Art. 33(4) PCT).

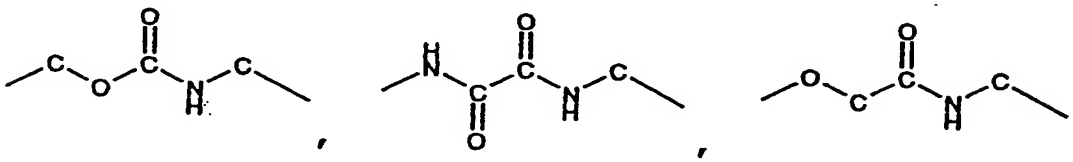
AMENDED CLAIMS

1. A pharmaceutical formulation comprising (i) a benzamide d rivative represented by the formula (1):



(1)

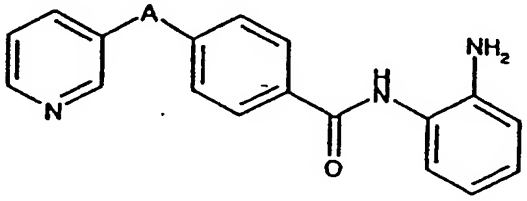
wherein A represents a structure shown by any one of the formula (2):



(2)

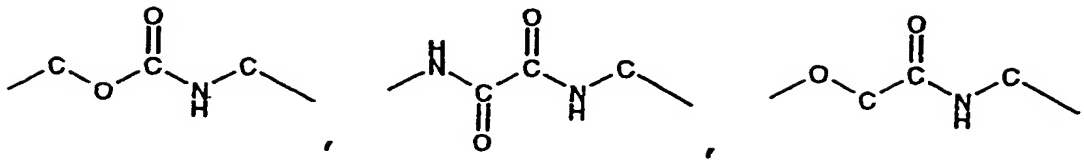
or a pharmaceutically acceptable salt thereof, (ii) one or more than one selected from the group consisting of an organic acid salt, an amino compound and an inorganic basic substance, and (iii) one or more than one selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent.

2. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

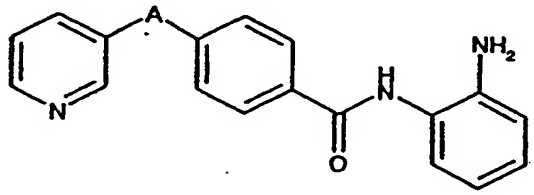
wherein A represents a structure shown by any one of the formula (2):



(2)

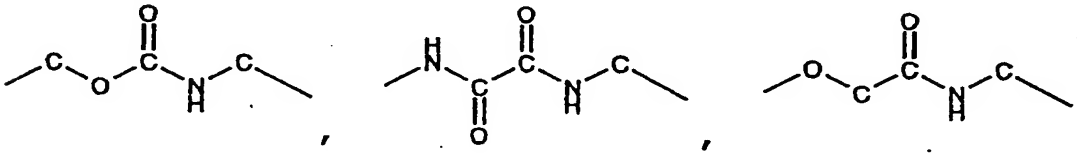
or a pharmaceutically acceptable salt thereof, and (ii) one or more than one selected from the group consisting of D-mannitol, partially gelatinized starch, carboxymethylstarch sodium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose and dimethylacetamide.

3. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

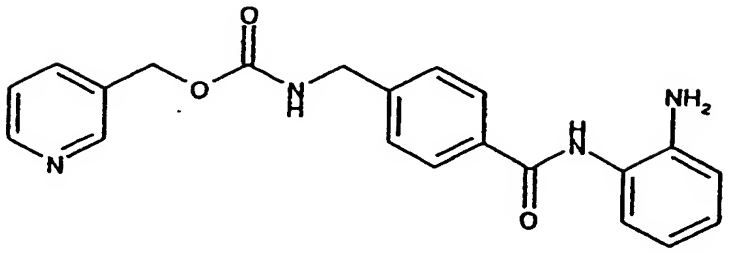
wherein A represents a structure shown by any one of the formula (2):



(2)

or a pharmaceutically acceptable salt thereof, wherein said benzamide derivative or pharmaceutically acceptable salt thereof is dissolved in propylene glycol.

4. The pharmaceutical formulation according to any one of claims 1 to 3 wherein said benzamide derivative is represented by the formula (3):



(3)

5. The pharmaceutical formulation according to claims 1, 2 and 4 wherein said pharmaceutical formulation is a solid formulation.

6. The pharmaceutical formulation according to claims 1 to 4 wherein said pharmaceutical formulation is a liquid formulation.

7. The pharmaceutical formulation according to claims 1, 4 and 5 wherein said excipient is D-mannitol.

8. The pharmaceutical formulation according to any one of claims 1, 4, 5 and 7 wherein said disintegrant is one or more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium.

9. The pharmaceutical formulation according to any one of claims 1, 4, 5, 7 and 8 wherein said binder is hydroxypropyl cellulose.

10. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 9 wherein said lubricant is one or more than one selected from magnesium stearate and talc.

11. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 10 wherein said coating agent is hydroxypropyl methylcellulose.

12. The pharmaceutical formulation according to claims 1, 4 and 6 wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol.

13. The pharmaceutical formulation according to claims 1 and 4 to 12 wherein said organic acid salt is

one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate.

14. The pharmaceutical formulation according to claims 1 and 4 to 13 wherein said amino compound is one or more than one selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate and carbachol.

15. The pharmaceutical formulation according to claims 1 and 4 to 14 wherein said inorganic basic substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

16. The pharmaceutical formulation according to claims 1, 2, 4, 5, 7 to 11 and 13 to 15 wherein the formulation is a solid formulation which comprises granules prepared by a dry granulation method.

17. The pharmaceutical formulation according to claims 1 to 4, 6 and 12 to 15 wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
sch10069pct		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 08011	16/08/2000	16/08/1999
Applicant		
SCHERING AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box !).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/EP 00/08011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4406 A61K47/06 A61K47/02 A61P35/00 A61P37/00
A61P1/00 A61P3/10 A61P5/00 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 847 992 A (MITSUI CHEMICALS INC.) 17 June 1998 (1998-06-17) claims 1,14-16,21-23 page 46, line 4 - line 40 & JP 10 152462 A 9 June 1998 (1998-06-09) cited in the application	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2000	10/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Siatou, E

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
/EP 00/08011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 847992 A	17-06-1998	JP 10152462 A	09-06-1998

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12193 A1

(51) International Patent Classification[7]: A61K 31/4406, 47/06, 47/02, A61P 35/00, 37/00, 1/00, 3/10, 5/00, 17/00

(21) International Application Number: PCT/EP00/08011

(22) International Filing Date: 16 August 2000 (16.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/229551 16 August 1999 (16.08.1999) JP

(71) Applicant *(for all designated States except US)*: **SCHERING AKTIENGESELLSCHAFT** [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE).

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(54) Title: PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE DERIVATIVE AS ACTIVE INGREDIENT

(57) Abstract: Stable pharmaceutical formulations can be obtained by mixing a pharmaceutically useful benzamide derivative or a pharmaceutically acceptable salt thereof with additives that do not easily produce degradation products, blending an organic acid salt, an amine compound, and an inorganic basic substance, producing solid formulations by the dry granulation method, and further adjusting the pH of the liquid formulations to 4 to 12. Pharmaceutical formulations that produce little degradation products and that are stable enough to be used as medical drugs can be obtained.

DESCRIPTION

PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE DERIVATIVE AS ACTIVE INGREDIENT

Field of Invention

The present invention relates to a pharmaceutical composition and in particular to a pharmaceutical formulations comprising as an active ingredient a benzamide derivative or a pharmaceutically acceptable salt thereof, that is useful as a pharmaceutical agent, in particular an anticancer agent.

Background Art

Benzamide derivatives or pharmaceutically acceptable salts thereof according to the present invention have an ability of inhibiting histone deacetylating enzymes and of inducing differentiation, and are useful as therapeutic or ameliorating agents for diseases that are involved in cellular growth such as malignant tumors, autoimmune diseases, skin diseases, infections, blood vessel diseases, allergic diseases, gastrointestinal disorders, hormonal diseases, diabetes mellitus, and the like, enhancers of the effect of gene therapy, or immunosuppressants. In particular, they are effective as anti-tumor agents and are effective against hematopoietic organ tumors and solid tumors (Japanese Unexamined Patent Publication (Kokai) No. 10-152462).

However, though the benzamide derivatives and pharmaceutically acceptable salts thereof of the present invention are stable per se, they become unstable and decompose markedly over time when combined with additives such as light silicic acid anhydride, lactose, corn starch, carboxymethyl cellulose, magnesium alminate metasilicate, titanium oxide, polyethylene glycols and polysorbates that are commonly used in order to produce dosage forms suitable for oral, percutaneous, or tissue administration.

Furthermore, when they are formulated into tablets

by the wet granulation, the most common granulation method of preparing solid formulations, they become further unstable and yield, in large quantities, decomposed products different from simple hydrolyzates, resulting in pharmaceutical formulations in which the ratio of an active ingredient is as low as about 0.001 to 25%, which noticeably decompose, and therefore which are unsuitable as pharmaceutical solid formulations to be provided as medical drugs. Also, pharmaceutical formulations that employ ingredients commonly used for liquids such as polysorbates, polyethylene glycols, and glycerin were unstable. Thus it was difficult to use, as medical drugs, pharmaceutical formulations that contain a benzamide derivative or a pharmaceutically acceptable salt thereof at about 0.001 to 25% as an active ingredient.

Disclosure of Invention

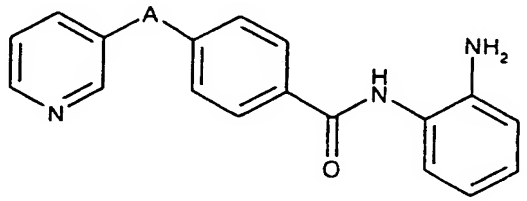
The present invention is intended to enhance the stability of compositions containing as an active ingredient a pharmaceutically useful benzamide derivative or a pharmaceutically acceptable salt and to effectively use them as a pharmaceutical formulation.

In order to solve the above problems, intensive research was conducted on the effects of temperature, humidity, and physicochemical properties on the solutions, powders, and solid shaped products to which a benzamide derivative or a pharmaceutically acceptable salt thereof has been added. As a result, the inventors have found that the problem of instability of an active ingredient can be solved and stable and excellent pharmaceutical formulations can be produced by using selectively, among the additives commonly used for pharmaceutical formulations, those additives that do not easily induce decomposition of benzamide derivatives, adding an organic acid salt, an amino compound and an inorganic basic substance, and the like as a stabilizer, producing using the dry granulation or adjusting pH in

the range of 4 to 12, preferably in the range of pH 7 to 11, and thereby have completed the present invention.

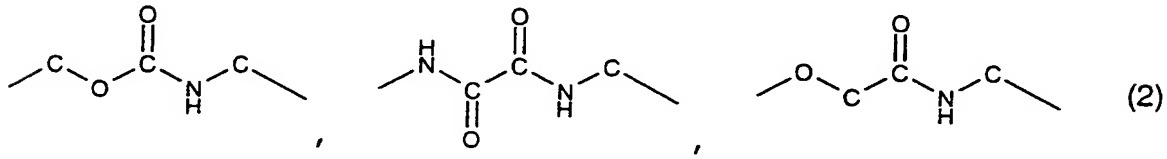
Thus, the present invention relates to

[1] a pharmaceutical formulation comprising a benzamide derivative represented by the formula (1):



(1)

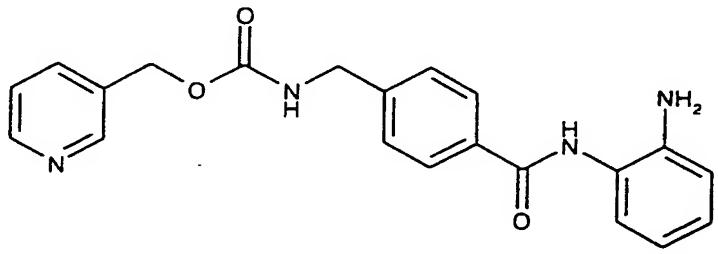
wherein A represents a structure shown by any one of the formula (2):



(2)

or a pharmaceutically acceptable salt thereof, and one or more than one additive selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent;

[2] as a preferred embodiment the pharmaceutical formulation of the above [1] wherein said benzamide derivative is represented by the formula (3);



(3)

[3] as a preferred embodiment the pharmaceutical formulation of the above [1] or [2] wherein said

excipient is D-mannitol;

[4] as another preferred embodiment the pharmaceutical formulation of any one of the above [1] to [3] wherein said disintegrant is one or more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium;

[5] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [4] wherein said binder is hydroxypropyl cellulose;

[6] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [5] wherein said lubricant is one or more than one selected from magnesium stearate and talc;

[7] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [6] wherein said coating agent is hydroxypropyl methylcellulose;

[8] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [7] wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol;

[9] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [8] wherein said formulation further comprises one or more than one selected from the group consisting of an organic acid salt, an amino compound, and an inorganic basic substance;

[10] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said organic acid salt is one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

[11] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said amino compound is one or more than one selected from

the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol;

[12] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said inorganic basic substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia;

[13] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [12] wherein the formulation is a solid formulation which comprises preparing granules by a dry granulation method; and

[14] as a preferred embodiment, the pharmaceutical formulation of any one of the above [1] to [13] wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

Embodiment for Carrying Out the Invention

The present invention will now be explained in further detail below.

The pharmaceutical formulations as used herein generally mean those that have been produced by formulating one or more additives with an active ingredient or active ingredients and that have been formulated into shapes suitable for use in various dosage forms of medical drugs.

According to the present invention, solid formulations, in particular powders, can be produced by adding to the active ingredient one or more than one additives that do not easily induce decomposition by using a method conventionally used by a person skilled in the art. Examples of additives that do not easily induce decomposition include: D-mannitol as an excipient; partly

pregelatinized starch, carboxymethylstarch sodium, and carmellose calcium as a disintegrant; hydroxypropyl cellulose as a binder; magnesium stearate and talc as a lubricant; and hydroxypropyl methyl cellulose as a coating agent. One or more than one of them can be used.

According to the present invention, solid formulations, in particular granules, tablets, and capsules can be produced by a dry granulation method in which additives that do not easily induce decomposition are added to the active ingredient, mixed in a shaker such as a granulator and a V-type mixer, compression-molded by a roller compactor after the mixture in a shaker, and further crushed by a power mill thereby to form granules.

Furthermore, more stable granules, tablets, and capsules can be obtained by adding to the active ingredient one or more than one selected from the group consisting of an organic acid salt such as monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate; an amino compound such as tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; an inorganic basic substance such as sodium carbonate, potassium carbonate, lithium carbonate, strontium carbonate; ammonium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, strontium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia, and by granulating in the dry granulation method.

When an organic acid salt, an amino compound or an inorganic basic substance is added, additives such as excipients, disintegrants, binders, lubricants, and coating agents can be used without limitation. Examples include, lactose, lactose anhydride, D-mannitol, corn

starch, and crystalline cellulose as an excipient; hydroxypropyl cellulose, polyvinylpyrrolidone, methyl cellulose, glycerin, and water as a binder; carmellose, calcium carmellose, low-substitution hydroxypropyl cellulose, and partly pregelatinized starch as a disintegrant; magnesium stearate, calcium stearate, stearic acid, and talc as a lubricant; and hydroxypropyl methyl cellulose, methacrylic acid copolymer, and hydroxypropyl methyl cellulose phthalate as a coating agent.

In accordance with the present invention, stable liquids, syrups, injections, emulsions, suspensions, suppositories, soft capsules whose contents are liquid, or hard capsules whose contents are liquid and the like can be produced by dissolving an active ingredient into solvents that do not easily induce the decomposition of the active ingredient such as propylene glycol and dimethylacetamide, by using a method conventionally used by a person skilled in the art.

More stable liquids, syrups, injections, emulsions, suspensions, suppositories, soft capsules whose contents are liquid, or hard capsules whose contents are liquid and the like can be produced by dissolving in a solvent one or more than one ingredients, selected from the group consisting of an organic acid salt such as monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate and trisodium citrate; an amine compound such as tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; an inorganic basic substance such as ammonium carbonate, disodium phosphate, sodium carbonate, potassium carbonate, lithium carbonate, strontium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, strontium bicarbonate, sodium hydroxide and ammonia, and by adjusting pH in the

range of 4 to 12 with an acid or a base.

As used herein, acids or bases mean organic bases, inorganic bases, organic acids, or inorganic acids that can be used as medical drugs. Organic bases mean tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, arginine, and the like. Inorganic bases mean sodium hydroxide, ammonium water, potassium bicarbonate, potassium carbonate, sodium bicarbonate, sodium carbonate, and the like. Organic acids mean citric acid, succinic acid, acetic acid, tartaric acid, lactic acid, and the like. Inorganic acids mean hydrochloric acid, sulfuric acid, phosphoric acid and the like.

In order to produce lyophilized formulations, according to the present invention, an active ingredient is mixed with a conventionally known solvent such as one or more than one solvent selected from the group consisting of purified water, macrogol, propylene glycol, polysorbate and dimethylacetamide; to a resulting composition are further added one or more than one additive selected from the group consisting of sugars; gelatin; dextrin; an organic acid salt such as monosodium fumarate, sodium alginate, sodium glutamate, sodium dehydroacetate, sodium erythorbate, trisodium citrate, and arginine-glutamate; an amine compound such as tris(hydroxymethyl)aminomethane, ammonia water, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, glycine, and carbachol; an inorganic basic substance such as ammonium carbonate, disodium phosphate, sodium carbonate, sodium bicarbonate and potassium bicarbonate; and then pH of the resulting composition is adjusted to 4 to 12, as desired, with an acid or a base, and the composition is freeze-dried under a reduced pressure.

The pharmaceutical formulations of the present

invention can be administered by any method depending on various dosage forms, the age and sex of the patient, the severity of disease, and other conditions. For example, tablets, pills, liquids, syrups, suspensions, emulsions, granules, and capsules may be orally administered, injections may be intravenously administered either singly or in an admixture with a conventional supplement such as glucose and an amino acid, and, as needed, may be administered singly intramuscularly, subcutaneously, or intraperitoneally. Lyophilized formulations reconstituted with solvent such as saline and purified water may be administered intravenously singly or in an admixture with a conventional supplement such as glucose, an amino acid and the like, and, as needed, may be administered singly intramuscularly, subcutaneously, or intraperitoneally. Suppositories may be directly administered intrarectally.

Dosages of the pharmaceutical formulations of the present invention are selected as appropriate depending on the method of administration, the age and sex of the patient, the severity of disease, and the like. Generally the daily dosage of an active ingredient compound is preferably in the range of about 0.0001 to 100 mg/kg, and for pharmaceutical formulations in the unit dosage form an active ingredient compound is preferably included at a range of about 0.001 to 1,000 mg.

Benzamide derivatives, active ingredients of the present invention, or pharmaceutically acceptable salts thereof can be produced by a method described in, for example, Japanese Unexamined Patent Publication (Kokai) No. 10-152462.

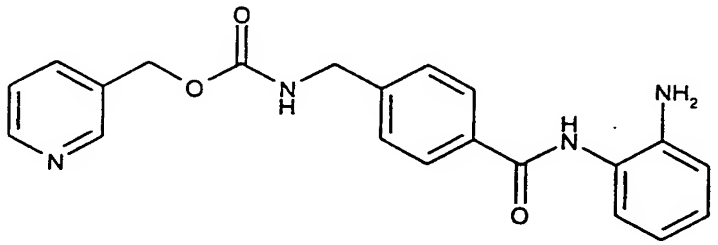
Medical drugs as used herein mean, in addition to anticancer agents, agents for the treatment and/or amelioration of autoimmune diseases, skin diseases, infections, diseases of blood vessels, allergic diseases, gastrointestinal disorders, hormonal diseases, diabetes

mellitus, and the like, enhancers of the effect of gene therapy, or immunosuppressants.

Examples

The present invention will now be explained in more detail with reference to the following compound, N-(2-aminophenyl)-4-[N-(pyridine-3-yl)methoxycarbonyl]aminomethyl benzamide (compound 1), in Examples and Reference Examples. It is to be noted, however, that the present invention is not limited by these examples in any way.

Compound 1



Example 1.

Compound 1 (1 g) was mixed with 1 g each of D-mannitol, partly pregelatinized starch, carmellose calcium, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate, and talc to prepare a powder formulation. Similarly, lactose, corn starch, crystalline cellulose, carmellose, light-weight silicic acid anhydride, magnesium aluminum metasilicate, and titanium oxide were mixed to prepare a comparative control sample. After these formulations were stored at an air-tight condition at 60°C for 4 weeks and at an open condition at 40°C and at a relative humidity of 75% for 3 months, they were subjected to HPLC analysis. The percentage (%) of degradation products relative to the active ingredient was shown in Table 1. The powder formulation prepared by mixing 1:1 with D-mannitol, partially gelatinized starch, carmellose calcium, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate or talc was stable.

Table (1): Stability of various powders

Additive	Storage condition	
	60°C air-tight 4 weeks	40°C 75% RH open 3 months
Comparative control sample		
None	0.18	0.19
Lactose	0.55	0.44
Corn starch	0.39	0.34
Crystalline cellulose	0.25	0.61
Carmellose	0.43	0.41
Light-weight silicic acid anhydride	5.87	10.01
Magnesium aluminum metasilicate	17.94	5.45
Titanium oxide	1.75	0.82
Example		
D-mannitol	0.21	0.21
Partially gelatinized starch	0.21	0.34
Carmellose calcium	0.30	0.21
Hydroxypropyl cellulose	0.20	0.20
Magnesium stearate	0.22	0.20
Hydroxypropyl methyl cellulose	0.27	0.21
Talc	0.36	0.23

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 2.

Pharmaceutical formulations a, b, c, d, e, and f shown in Table (2) were prepared in the following procedure. Thus, compound 1 and D-mannitol divided into 1/8, 2/8, and 5/8 of the prescribed amount were serially added under mixing using a granulator to prepare homogeneous powders. Furthermore, 1/2 of the prescribed amount of magnesium stearate was added thereto and was mixed in a V-shaped mixer for 20 minutes, compression-molded by a roller compactor, and further crushed by a power mill to prepare granules. Subsequently, carboxymethyl starch sodium of the prescribed amount and 1/2 of the prescribed amount of magnesium stearate were added and mixed in a V-shaped mixer, made into tablets by tabletting machine to obtain samples a, b, c, d, e, and f.

Table (2): Formulation for tablets (unit: mg)

Ingredient/number	Sample of the present invention					
	a	b	c	d	e	f
Active ingredient	5.0	1.0	1.0	1.0	1.0	1.0
D-mannitol	56.0	60.0	60.0	60.0	60.0	60.0
Carboxymethyl starchsodium	3.3	3.3	3.3	3.3	3.3	3.3
Magnesium stearate	0.7	0.7	0.7	0.7	0.7	0.7
Tris(hydroxymethyl) aminomethane	-	-	0.5	-	-	-
Potassium bicarbonate	-	-	-	0.5	-	-
Sodium carbonate	-	-	-	-	0.5	-
Potassium carbonate	-	-	-	-	-	0.5
Total	65.0	65.0	65.5	65.5	65.5	65.5

Reference Example 1.

D-mannitol, partially gelatinized starch, carmellose calcium, magnesium stearate, hydroxypropyl cellulose, polyvinylpyrrolidone K30, or the like which is comparatively stable when mixed with Compound 1 was granulated according to the formulation shown in Table (3) by the wet granulation method and made into tablets by tabletting machine to obtain samples g to i.

Table (3): Formulation for tablets (unit: mg)

Ingredient/number	Sample		
	g	h	i
Active ingredient	1.0	1.0	1.0
D-mannitol	40.6	40.6	40.6
Partially gelatinized starch	17.4	17.4	17.4
Hydroxypropyl cellulose	2.0	2.0	-
Polyvinylpyrrolidone	-	-	2.0
Carmellose calcium	3.3	-	3.3
Magnesium stearate	0.7	0.7	0.7
Total	65.0	65.0	65.0

The percentage (%) of degradation products of compound 1 is shown in Table 4, when samples obtained in Example 2 and Reference Example 1 were stored at an air-tight condition at 60°C for 4 weeks and at an air-tight condition at 80°C for 3 days, and then were subjected to HPLC analysis. The pharmaceutical formulations containing 1 mg of an active ingredient obtained by the wet granulation method shown in Reference Example 1 were unstable as they produced degradation products other than the hydrolyzates, while the samples of the present

invention shown in Example 2, both 5.0 mg- and 1.0 mg-containing formulations, were stable as the production of degradation products remained low.

Table (4): Stability of tablets containing compound 1

Sample		Content (mg)	Storage condition 60°C air-tight 4 weeks (%)	80°C air-tight 3 days (%)
The invention sample	a	5.0	0.4	0.4
	b	1.0	1.0	1.3
	c	1.0	0.7	0.5
	d	1.0	-	0.4
	e	1.0	-	0.4
	f	1.0	-	0.4
Reference example	g	1.0	4.1	3.0
	h	1.0	4.5	2.1
	i	1.0	5.8	5.3

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 3.

Compound 1 was dissolved to a concentration of 20 mg/ml in propylene glycol or dimethylacetamide to prepare liquid formulations. As comparative control samples, compound 1 was dissolved to a concentration of 20 mg/ml in polysorbate 80 or polyethylene glycol 400. Table (5) shows the percentage (%) of degradation products of compound 1 when these formulations were stored at an air-tight condition at 80°C for 3 days. They exhibited good stability when dissolved in propylene glycol or dimethylacetamide.

Table (5): Stability when dissolved in various solvents

Additive	Amount of degradation products (%)
Polysorbate 80	18.1
Polyethylene glycol 400	41.4
Dimethylacetamide	4.1
Propylene glycol	3.6

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 4.

Compound 1 was dissolved to a concentration of 20 mg/ml in polyethylene glycol 400 to prepare a liquid formulation, which was set as a comparative control sample. To the comparative control sample was added each additive at a concentration of 0.05 M to prepare the liquid formulation of the present invention. Table (6) shows the percentage (%) of degradation products of the active ingredients when these formulations and the comparative control samples were stored at an air-tight condition at 80°C for 3 days. Stability was enhanced in the samples to which an organic acid salt, an amino compound, or an inorganic basic substance of the present invention was added.

Table (6): Stability of liquid formulations in which each additive was blended at 0.05 M to compound 1 at 20 mg/ml polyethylene glycol 400
(Storage condition: 80°C, air tight, Storage period: 3 days)

	Additive	Amount of degradation products (%)	pH
Comparative control sample	None	41.4	5.3
The invention sample	Sodium fumarate	21.6	7.0
	Sodium alginate	23.7	6.7
	Sodium dehydroacetate	13.0	8.6
	Sodium erhysorbate	13.2	7.3
	Trisodium citrate	28.2	8.0
	Tris(hydroxymethyl)aminomethane	2.9	10.1
	Monoethanolamine	4.3	11.5
	Diethanolamine	3.9	11.7
	Triethanolamine	9.6	9.4
	Diisopropanolamine	4.7	9.9
	Triisopropanolamine	16.5	8.3
	Dihydroxyaluminum aminoacetate	7.3	6.4
	L-arginine	10.6	11.5
	Creatinine	18.6	7.0
	Sodium glutamate	23.1	-
	Glycine	26.7	-
	L-arginine L-glutamate	29.4	6.5
	Carbachol	32.3	5.4
	Ammonium carbonate	3.6	10.7
	Disodium phosphate	10.8	7.6
	Sodium carbonate	16.8	10.1
	Sodium bicarbonate	25.0	6.5
	Potassium bicarbonate	15.5	7.0
	Ammonia	4.6	11.7

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 5.

To compound 1 dissolved at a concentration of 20 mg/ml in polyethylene glycol 400 was added an equal volume of 0.1 M tris(hydroxymethyl)aminomethane buffer of which pH is varied with hydrochloric acid or sodium hydroxide to prepare a liquid formulation of compound 1 at 10 mg/ml. Table 7 shows the percentage of the degradation products of the active ingredient when these formulations were stored at an air-tight condition at

80°C for 3 days. Samples of the present invention of which pH was adjusted in the range of 7 to 11 exhibited good stability.

Table (7): Stability of 10 mg/ml polyethylene glycol 400 solution of compound 1 when pH was varied (storage condition: 80°C, air-tight, storage period: 3 days)

pH	Amount of degradation products (%)
3.8	98.6
13.2	48.8
7.3	11.9
7.7	8.2
8.5	5.8
9.5	5.6
10.1	4.4

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 6.

Compound 1 was dissolved at a concentration of 20 mg/ml in polyethylene glycol 400, and sodium hydroxide was added thereto so that the final various concentrations can be from 0 mM to 10 mM to prepare liquid formulations. Table 8 shows the percentage of the degradation products of the active ingredient when these formulations were stored at each pH of these formulations and at an air-tight condition at 80°C for 1 day or 7 days. Samples of the present invention of which pH was adjusted in the range of about 7 to 11 exhibited good stability.

Table (8): Relationship between pH and stability of liquid formulations in which compound 1 was dissolved at 20 mg/ml in polyethylene glycol 400, and then sodium hydroxide was added thereto (storage condition: 80°C, air-tight, storage period: 1 day or 7 days)

Concentration of sodium hydroxide (mM)	pH	Amount of degradation products (%)	
		80°C - 1 day	80°C - 7 days
0	5.3	16.0	63.7
0.01	5.9	14.1	60.6
0.1	6.1	14.3	56.0
1.0	7.3	9.7	33.7
2.0	8.9	4.6	12.4
3.0	9.4	5.0	9.8
4.0	10.4	6.0	9.7
5.0	10.8	9.7	11.4
10.0	13.1	71.5	90.6

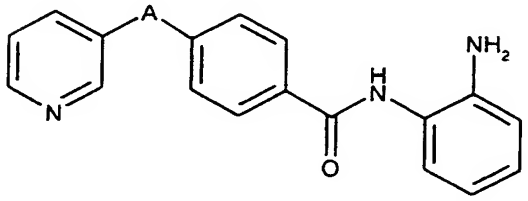
Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Industrial Applicability

Pharmaceutical formulations that produce little degradation products and that are stable enough to be used as medical drugs can be obtained by mixing a pharmaceutically useful benzamide derivatives or a pharmaceutically acceptable salt thereof with additives that do not easily produce degradation products, blending an organic acid salt, an amine compound, or an inorganic basic substance, producing solid formulations by the dry granulation method, and further adjusting the pH of the liquid formulations to 4 to 12.

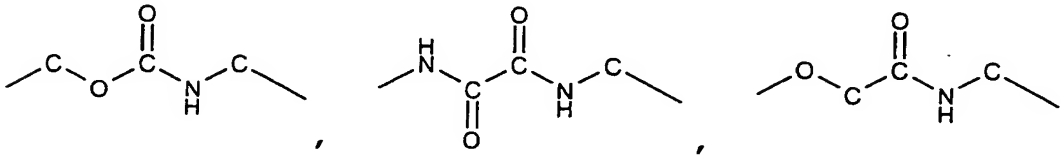
CLAIMS

1. A pharmaceutical formulation comprising a benzamide derivative represented by the formula (1):



(1)

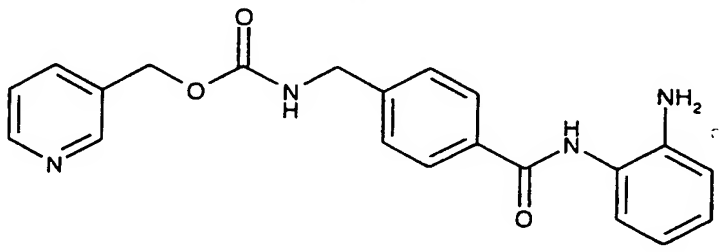
wherein A represents a structure shown by any one of the formula (2):



(2)

or a pharmaceutically acceptable salt thereof, and one or more than one additive selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent.

2. The pharmaceutical formulation according to claim 1 wherein said benzamide derivative is represented by the formula (3):



(3)

3. The pharmaceutical formulation according to claim 1 or 2 wherein said excipient is D-mannitol.

4. The pharmaceutical formulation according to any one of claims 1 to 3 wherein said disintegrant is one or

more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium.

5. The pharmaceutical formulation according to any one of claims 1 to 4 wherein said binder is hydroxypropyl cellulose.

6. The pharmaceutical formulation according to any one of claims 1 to 5 wherein said lubricant is one or more than one selected from magnesium stearate and talc.

7. The pharmaceutical formulation according to any one of claims 1 to 6 wherein said coating agent is hydroxypropyl methylcellulose.

8. The pharmaceutical formulation according to any one of claims 1 to 7 wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol.

9. The pharmaceutical formulation according to any one of claims 1 to 8 wherein said formulation further comprises one or more than one selected from the group consisting of an organic acid salt, an amino compound, and an inorganic basic substance.

10. The pharmaceutical formulation according to any one of claims 1 to 9 wherein said organic acid salt is one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate.

11. The pharmaceutical formulation according to any one of claims 1 to 9 wherein said amino compound is one or more than one selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate and carbachol.

12. The pharmaceutical formulation according to any one of claims 1 to 9 wherein said inorganic basic

substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

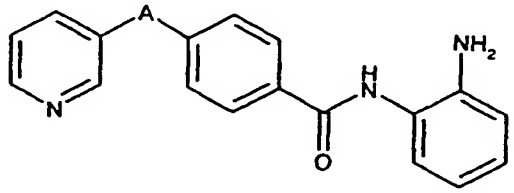
13. The pharmaceutical formulation according to any one of claims 1 to 12 wherein the formulation is a solid formulation which comprises granules prepared by a dry granulation method.

14. The pharmaceutical formulation according to any one of claims 1 to 13 wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

AMENDED CLAIMS

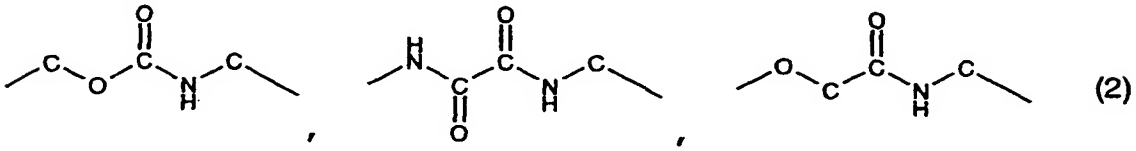
[received by the International Bureau on 10 January 2001 (10.01.01);
original claims 1 - 14 replaced by new claims 1 – 17 (4 pages)]

1. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

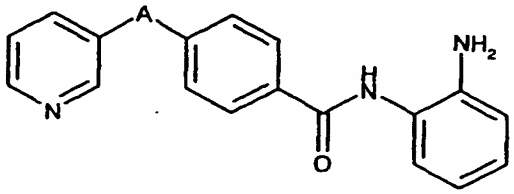
wherein A represents a structure shown by any one of the formula (2):



(2)

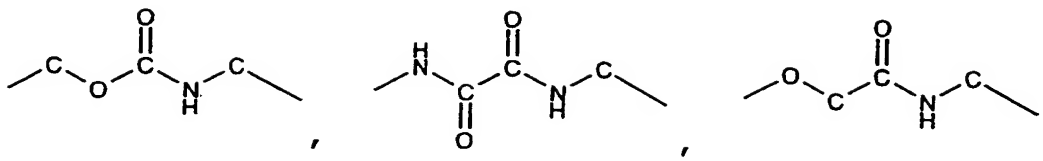
or a pharmaceutically acceptable salt thereof, (ii) one or more than one selected from the group consisting of an organic acid salt, an amino compound and an inorganic basic substance, and (iii) one or more than one selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent.

2. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

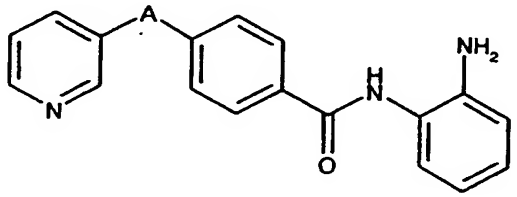
wherein A represents a structure shown by any one of the formula (2):



(2)

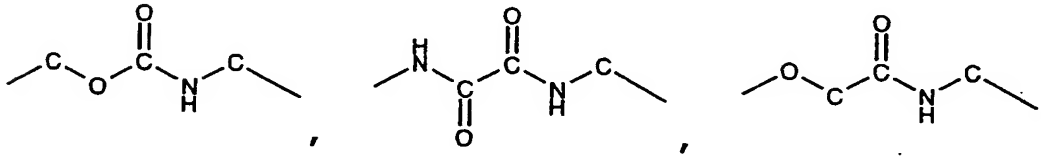
or a pharmaceutically acceptable salt thereof, and (ii) one or more than one selected from the group consisting of D-mannitol, partially gelatinized starch, carboxymethylstarch sodium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose and dimethylacetamide.

3. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

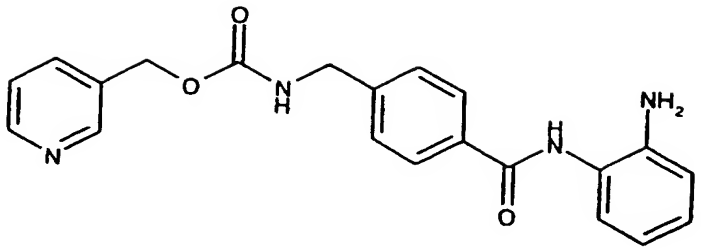
wherein A represents a structure shown by any one of the formula (2):



(2)

or a pharmaceutically acceptable salt thereof, wherein said benzamide derivative or pharmaceutically acceptable salt thereof is dissolved in propylene glycol.

4. The pharmaceutical formulation according to any one of claims 1 to 3 wherein said benzamide derivative is represented by the formula (3):



(3)

5. The pharmaceutical formulation according to claims 1, 2 and 4 wherein said pharmaceutical formulation is a solid formulation.

6. The pharmaceutical formulation according to claims 1 to 4 wherein said pharmaceutical formulation is a liquid formulation.

7. The pharmaceutical formulation according to claims 1, 4 and 5 wherein said excipient is D-mannitol.

8. The pharmaceutical formulation according to any one of claims 1, 4, 5 and 7 wherein said disintegrant is one or more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium.

9. The pharmaceutical formulation according to any one of claims 1, 4, 5, 7 and 8 wherein said binder is hydroxypropyl cellulose.

10. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 9 wherein said lubricant is one or more than one selected from magnesium stearate and talc.

11. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 10 wherein said coating agent is hydroxypropyl methylcellulose.

12. The pharmaceutical formulation according to claims 1, 4 and 6 wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol.

13. The pharmaceutical formulation according to claims 1 and 4 to 12 wherein said organic acid salt is

one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate.

14. The pharmaceutical formulation according to claims 1 and 4 to 13 wherein said amino compound is one or more than one selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate and carbachol.

15. The pharmaceutical formulation according to claims 1 and 4 to 14 wherein said inorganic basic substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

16. The pharmaceutical formulation according to claims 1, 2, 4, 5, 7 to 11 and 13 to 15 wherein the formulation is a solid formulation which comprises granules prepared by a dry granulation method.

17. The pharmaceutical formulation according to claims 1 to 4, 6 and 12 to 15 wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4406 A61K47/06 A61K47/02 A61P35/00 A61P37/00
A61P1/00 A61P3/10 A61P5/00 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 847 992 A (MITSUI CHEMICALS INC.) 17 June 1998 (1998-06-17) claims 1,14-16,21-23 page 46, line 4 - line 40 & JP 10 152462 A 9 June 1998 (1998-06-09) cited in the application	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2000	10/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/08011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 847992 A	17-06-1998	JP 10152462 A	09-06-1998